AMENDMENTS TO THE CLAIMS

1. (Currently amended) A method for screening a plurality of test substances useful as a preventive or therapeutic agent for ~~the prevention or treatment of~~ a disease involving an oxidative stress, which comprises the steps of

i) testing each of the test substances ~~for its ability~~ to determine if it inhibits ~~inhibit the~~ an activity of a GADD34L protein and

ii) identifying the test substance which inhibits the activity of said GADD34L protein, ~~thereby to identify~~ and selecting as a test substance useful as a preventive or therapeutic agent for a disease involving an oxidative stress each test substance that inhibits the activity of said GADD34L protein.

2. (Currently amended) A method for identifying a test substance useful as a preventive or therapeutic agent for ~~the prevention or treatment of~~ a disease involving an oxidative stress, which comprises testing a test substance ~~for its ability~~ to determine if it inhibits ~~inhibit the~~ an activity of a GADD34L protein, thereby to determine whether the test substance promotes resistance to cell stress, and to identify said test substance as a preventive or therapeutic agent for a disease involving an oxidative stress.

3. (Currently amended) The method according to claim 1 or 2, wherein the test substance inhibits ~~the~~ an activity of ~~the~~ a GADD34L protein by disrupting formation of ~~the~~ a protein complex by the GADD34L protein and a PP1c protein ~~complex~~.

4. (Currently amended) The method according to claim 1 or 2, wherein the test substance inhibits ~~the~~ an activity of a GADD34L protein by inhibiting ~~the~~ production of the GADD34L protein from ~~the~~ a GADD34L mRNA.

5. (Currently amended) The method according to claim 1 or 2, wherein the test substance inhibits ~~the~~ an activity of a GADD34L protein by inhibiting ~~the~~ production of a GADD34L mRNA from a GADD34L genomic locus.

6. (Previously presented) The method according to claim 2, further comprising a step of verifying whether said test substance does not cause stress to cells.

7. (Currently amended) The method according to claim 1 or 2, which comprises the steps of

i) contacting ~~the~~ a test substance or each of the test substances with a cell-free composition ~~containing~~ comprising a GADD34L protein and a PP1c protein ~~proteins~~ in the form of a purified complex and an eIF2α protein in a phosphorylated form,

ii) assessing ~~the~~ a level of phosphorylation of the eIF2α protein in comparison with the level of phosphorylation of the eIF2α protein determined in the absence of the test substance or each of the test substances, in a cell-free composition ~~containing~~ comprising a GADD34L protein and a PP1c protein ~~proteins~~ in the form of a purified complex and an eIF2α protein in a phosphorylated form, and

iii) identifying the test substance which provides a higher level of phosphorylation of the eIF2α protein, in comparison with the level of phosphorylation of the eIF2α protein determined in the absence of the test substance or each of the test substances, thereby to identify a test substance useful as a preventive or therapeutic agent for a disease involving an oxidative stress.

8. (Currently amended) The method according to claim 7, wherein ~~the assessment of~~ ~~the~~ assessing a level of phosphorylation of the eIF2α protein is effected by an immunoassay using an antibody that specifically recognizes ~~the~~ a phosphorylated form of the eIF2α protein.

9. (Currently amended) The method according to claim 7, wherein ~~the assessment of the~~ assessing a level of phosphorylation of the eIF2α protein is effected by assessing ~~tracking the~~ covalent binding of a radiolabelled phosphate group to the eIF2α protein.

10. (Currently amended) The method according to claim 1 or 2, which comprises the steps of

i) contacting a test substance or each of the test substances with a cell ~~cells~~ not subject to stress that ~~contain~~ comprises a PP1c protein and an eIF2α protein and that ~~overexpress~~ overexpresses a GADD34L protein, or a portion ~~portions~~ thereof,

ii) assessing ~~the~~ a level of phosphorylation of the eIF2α protein after contact with the test substance or each of the test substances, in comparison with ~~the~~ a level of ~~eIF2α~~ phosphorylation of the eIF2α protein in the absence of the test substance or each of the test substances, and

iii) identifying the test substance which provides a higher level of phosphorylation of the eIF2α protein, in comparison with ~~the~~ a level of phosphorylation of the eIF2α protein determined in the absence of test substance, thereby to identify a test substance useful as a preventive or therapeutic agent for a disease involving an oxidative stress.

11. (Currently amended) The method according to claim 10, wherein ~~the assessment of the~~ assessing a level of phosphorylation of the eIF2α protein is effected by an immunoassay using an antibody that specifically recognizes ~~the~~ a phosphorylated form of the eIF2α protein.

12. (Currently amended) The method according to claim 10, wherein ~~the assessment of the~~ assessing a level of phosphorylation of the eIF2α protein is effected by assessing ~~tracking the~~ covalent binding of a radiolabelled phosphate group to the eIF2α protein.

13. (Currently amended) The method according to claim 1 or 2, which comprises the steps of,

i) contacting a test substance or each of the test substances with a cell ~~cells~~ that ~~normally express~~ expresses an endogenous GADD34L,

ii) and identifying a test substance that inhibits the expression of the endogenous GADD34L, thereby to identify a test substance useful as a preventive or therapeutic agent for a disease involving an oxidative stress.

14. (Currently amended) The method according to claim 13, wherein ~~the~~ a level of ~~GADD34L~~ expression of the endogenous GADD34L is assessed by determining ~~the~~ a level of transcription of the endogenous GADD34L.

15. (Currently amended) The method according to claim 14, wherein ~~determination of the~~ determining a level of transcription of the endogenous GADD34L is effected by means of a Northern blot.

16. (Currently amended) The method according to claim 14, wherein ~~determination of the~~ determining a level of transcription of the endogenous GADD34L is effected by means of *in situ* hybridization.

17. (Currently amended) The method according to claim 13, wherein ~~the~~ a level of ~~GADD34L~~ expression of the endogenous GADD34L is assessed by ~~the~~ determining a level of translation of the endogenous GADD34L.

18. (Currently amended) The method according to claim 17, wherein determining a ~~determination of the~~ level of translation of the endogenous GADD34L is effected by means of an immunoassay.

19. (Currently amended) The method according to claim 1 or 2, which comprises the steps of

i) contacting a test substance or each of the test substances with a cell ~~cells~~ not subject to stress that ~~overexpress~~ overexpresses a GADD34L protein, or a portion ~~portions~~ thereof,

ii) assessing an expression level ~~the expression of expression~~ of a target gene, and

iii) identifying a test substance that ~~activates~~ increases the expression level of the target gene, thereby to identify a test substance useful as a preventive or therapeutic agent for a disease involving an oxidative stress.

20. (Currently amended) The method according to claim 19, where the target gene is ~~the~~ a CHOP gene.

21. (Currently amended) The method according to claim 1 or 2, which comprises the steps of,

i) ~~obtaining~~ providing a cell ~~cells~~ not subject to stress that ~~overexpress~~ overexpresses a GADD34L protein, or ~~portions~~ a portion thereof, ~~and have been transfected with~~ and which comprises a reporter gene operatively associated with all or part of ~~the~~ a promoter of a target gene,

ii) contacting a test substance or each of the test substances with the cell ~~these cells~~, and assaying ~~the~~ a level of expression of said reporter gene, and

iii) identifying a test substance that ~~activates~~ increases the expression level of the reporter gene, thereby to identify a test substance useful as a preventive or therapeutic agent for a disease involving an oxidative stress.

22. (Currently amended) The method according to claim 21, where the target gene is ~~the~~ a CHOP gene.

23. (Currently amended) The method according to claim 21, wherein said reporter gene ~~encodes one of~~ is selected from the group consisting of GFP, CAT, GAL, LUC, and GUS.

24. (Currently amended) The method according to claim 1 or 2, which comprises the steps of,

i) ~~obtaining~~ providing a cell ~~cells~~ not subject to stress that ~~overexpress~~ overexpresses a GADD34L protein, or ~~portions~~ a portion thereof,

ii) contacting a test substance or each of the test substances with the cell ~~cells~~, in the presence of a toxic agent that induces oxidative stress,

iii) quantitating cell survival of the cell ~~cells that overexpress GADD34L, or portions of GADD34L,~~ following exposure to the toxic agent in the presence and absence of the test substance or each of the test substances , and

iv) identifying a test substance that promotes cell survival of the cell ~~cells~~ following exposure to ~~concentrations~~ a concentration of the toxic agent that ~~induce~~ induces oxidative stress, thereby to identify a test substance useful as a preventive or therapeutic agent for a disease involving an oxidative stress.

25. (Currently amended) The method according to claim 24 wherein the toxic agent ~~which~~ that induces oxidative stress is tunicamycin, arsenite, or glutamate.

26. (Currently amended) The method according to claim 1 or 2, wherein the disease involving an oxidative stress is ~~identified test substance is useful for the prevention or treatment of a disease involving~~ neuronal ischemia.

27. (Currently amended) The method according to claim 1 or 2, wherein the disease involving an oxidative stress is ~~identified test substance is useful for the prevention or treatment of a disease involving~~ heart ischemia.

28. (Currently amended) The method according to claim 1 or 2, wherein the disease involving an oxidative stress is ~~identified test substance is useful for the prevention or treatment of~~ renal damage induced by ischemia or toxins.

29. (Currently amended) The method according to claim 1 or 2, wherein the disease involving an oxidative stress is ~~identified test substance is useful for the prevention or treatment of~~ an ~~auto-immune~~ autoimmune disease.

30. (Currently amended) The method according to claim 1 or 2, wherein the disease involving an oxidative stress is ~~selected compound is useful for the prevention or treatment of~~ a neurodegenerative disorder.

31. (Currently amended) A method for the prevention or treatment of a disease involving an oxidative stress in a patient in need of such treatment, which comprises administering to the patient an effective amount of a ~~GADD34L inhibitor identified for its ability to promote resistance to cell stress while not causing stress~~ substance identified as a preventive or therapeutic agent for a disease involving an oxidative stress according to the method of claim 1 or 2.

32. (Currently amended) A method of claim 31, wherein the disease involving an oxidative stress is ~~a disease involving~~ neuronal ischemia, ~~a disease involving~~ heart ischemia, ~~a disease involving~~ renal damage induced by ischemia or toxins, an ~~auto-immune~~ autoimmune disease, or a neurodegenerative disorder.

33. (Currently amended) The method according to ~~claim 3~~ claim 1, further comprising a step of verifying whether said test substance does not cause stress to cells.

34. (New) A method to identify a test substance useful as a substance that promotes resistance to cell stress, which comprises: i) testing a test substance to determine if it inhibits an activity of a GADD34L protein, and; ii) identifying the test substance which inhibits the activity of said GADD34L protein, and selecting as a test substance that promotes resistance to cell stress each test substance that inhibits the activity of said GADD34L protein.

35. (New) The method according to claim 34, wherein the test substance inhibits an activity of a GADD34L protein by disrupting formation of a protein complex by the GADD34L protein and a PP1c protein.

36. (New) The method according to claim 34, wherein the test substance inhibits an activity of a GADD34L protein by inhibiting production of the GADD34L protein from a GADD34L mRNA.

37. (New) The method according to claim 34, wherein the test substance inhibits an activity of a GADD34L protein by inhibiting production of a GADD34L mRNA from a GADD34L genomic locus.

38. (New) The method according to claim 34, further comprising a step of verifying whether said test substance does not cause stress to cells.

39. (New) The method according to claim 34, which comprises the steps of

i) contacting a test substance with a cell-free composition comprising a GADD34L protein and a PP1c protein in the form of a purified complex and an eIF2α protein in a phosphorylated form,

ii) assessing a level of phosphorylation of the eIF2α protein in comparison with the level of phosphorylation of the eIF2α protein determined in the absence of the test substance, in a cell-free composition comprising a GADD34L protein and a PP1c protein in the form of a purified complex and an eIF2α protein in a phosphorylated form, and

iii) identifying the test substance which provides a higher level of phosphorylation of the eIF2α protein, in comparison with the level of phosphorylation of the eIF2α protein determined in the absence of the test substance, thereby to identify said substance as a substance that promotes resistance to cell stress.

40. (New) The method according to claim 39, wherein assessing a level of phosphorylation of the eIF2α protein is effected by an immunoassay using an antibody that specifically recognizes a phosphorylated form of the eIF2α protein.

41. (New) The method according to claim 39, wherein assessing a level of phosphorylation of the eIF2α protein is effected by assessing covalent binding of a radiolabelled phosphate group to the eIF2α protein.

42. (New) The method according to claim 34, which comprises the steps of

i) contacting a test substance with a cell not subject to stress that comprises a PP1c protein and an eIF2α protein and that overexpresses a GADD34L protein, or a portion thereof,

ii) assessing a level of phosphorylation of the eIF2α protein after contact with the test substance, in comparison with a level of phosphorylation of the eIF2α protein in the absence of the test substance, and

iii) identifying the test substance which provides a higher level of phosphorylation of the eIF2α protein, in comparison with a level of phosphorylation of the eIF2α protein determined in the absence of test substance, thereby to identify said substance as a substance that promotes resistance to cell stress.

43. (New) The method according to claim 42, wherein assessing a level of phosphorylation of the eIF2α protein is effected by an immunoassay using an antibody that specifically recognizes a phosphorylated form of the eIF2α protein.

44. (New) The method according to claim 42, wherein assessing a level of phosphorylation of the eIF2α protein is effected by assessing covalent binding of a radiolabelled phosphate group to the eIF2α protein.

45. (New) The method according to claim 34, which comprises the steps of,

i) contacting a test substance with a cell that expresses an endogenous GADD34L,

ii) and identifying a test substance that inhibits the expression of the endogenous GADD34L, thereby to identify said substance as a substance that promotes resistance to cell stress.

46. (New) The method according to claim 45, wherein a level of expression of the endogenous GADD34L is assessed by determining a level of transcription of the endogenous GADD34L.

47. (New) The method according to claim 46, wherein determining a level of transcription of the endogenous GADD34L is effected by means of a Northern blot.

48. (New) The method according to claim 46, wherein determining a level of transcription of the endogenous GADD34L is effected by means of *in situ* hybridization.

49. (New) The method according to claim 45, wherein a level of expression of the endogenous GADD34L is assessed by determining a level of translation of the endogenous GADD34L.

50. (New) The method according to claim 49, wherein determining a level of translation of the endogenous GADD34L is effected by means of an immunoassay.

51. (New) The method according to claim 34, which comprises the steps of

i) contacting a test substance with a cell not subject to stress that overexpresses a GADD34L protein, or a portion thereof,

ii) assessing an expression level of a target gene, and

iii) identifying a test substance that increases the expression level of the target gene, thereby to identify said substance as a substance that promotes resistance to cell stress.

52. (New) The method according to claim 51, where the target gene is a CHOP gene.

53. (New) The method according to claim 34, which comprises the steps of,

i) providing a cell not subject to stress that overexpresses a GADD34L protein, or a portion thereof, and which comprises a reporter gene operatively associated with all or part of a promoter of a target gene,

ii) contacting a test substance with the cell, and assaying a level of expression of said reporter gene, and

iii) identifying a test substance that increases the expression level of the reporter gene, thereby to identify said substance as a substance that promotes resistance to cell stress.

54. (New) The method according to claim 53, where the target gene is a CHOP gene.

55. (New) The method according to claim 53, wherein said reporter gene is selected from the group consisting of GFP, CAT, GAL, LUC, and GUS.

56. (New) The method according to claim 34, which comprises the steps of,

i) providing a cell not subject to stress that overexpresses a GADD34L protein, or a portion thereof,

ii) contacting a test substance with the cell, in the presence of a toxic agent that induces oxidative stress,

iii) quantitating cell survival of the cell following exposure to the toxic agent in the presence and absence of the test substance, and

iv) identifying a test substance that promotes cell survival of the cell following exposure to a concentration of the toxic agent that induces oxidative stress, thereby to identify said substance as a substance that promotes resistance to cell stress.

57. (New) The method according to claim 56 wherein the toxic agent that induces oxidative stress is tunicamycin, arsenite, or glutamate.

58. (New) A method to promote resistance to cell stress in a patient in need of such treatment, which comprises administering to the patient an effective amount of a substance that promotes resistance to cell stress identified according to the method of claim 34.

59. (New) The method of claim 58, wherein the patient is a patient having a disease involving an oxidative stress.

60. (New) The method of claim 59, wherein the disease involving an oxidative stress is neuronal ischemia, heart ischemia, renal damage induced by ischemia or toxins, an autoimmune disease, or a neurodegenerative disorder.

61. (New) A method to promote resistance to cell stress comprising contacting a cell with an effective amount of a substance that promotes resistance to cell stress identified according to the method of claim 34.

62. (New) A method to promote resistance to cell stress comprising contacting a cell with an effective amount of a substance identified as a preventive or therapeutic agent for a disease involving an oxidative stress according to the method of claim 1 or 2.